Wistar rats (200 g) were obtained from Charles River Laboratories. Rats were treated with 3mg/kg mastoparan by intravenous injection in the tail vein, immediately followed by 15 mg/kg lead acetate and 5 μg/kg LPS 0111:B4 intravenously. Mortality was assessed up to 96 hours following LPS treatment. Mortality frequency was compared by Fisher exact test and statistical analysis was performed using Yates corrected Chi square test.--

Please replace the paragraph beginning at page 11, line 24, with the following:

--**Example 1. Association of CD14 with G Proteins Following LPS Stimulation**

To elucidate the mechanism of LPS-induced signal transduction mediated through CD14, CD14 was immunoprecipitated from freshly isolated human monocytes and *in vitro* kinase assays performed to assess the association of CD14 with phosphorylated proteins.--

In the Claims:

Please amend claims 1 and 11 as follows:

1. **(Amended)** A method for treating or preventing septic shock in a subject comprising administering to the subject an effective amount of an agent which binds G protein, to thereby inhibit the interaction of said G protein with CD14, such that septic shock in the subject is treated or prevented.

11. **(Amended)** A composition for treating or preventing septic shock in a subject comprising an effective amount of an agent which binds G protein to thereby inhibit the interaction of said G protein and CD14, such that septic shock in the subject is treated or prevented.

REMARKS

Claims 1-17 were pending in the application. Claims 1 and 11 have been amended. No claims have been added or canceled. Accordingly, claims 1-17 remain pending in the instant application.

No new matter has been added. Support for the amendments to claims 1 and 11 can be found throughout the instant specification. The amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim Applicants' invention in order to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

For the Examiner's convenience, a copy of the pending claims is attached hereto as Appendix A. Also attached hereto is a marked-up version of the changes made to the specification and the claims by the current amendments. The attached page is captioned "Version With Markings to Show Changes Made".

Rejection Under 35 U.S.C. § 119(e)

The Examiner states that the "Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e)."

Applicants have amended the specification to insert a specific reference to the prior application(s) in the first sentence of the specification as required by 37 CFR 1.78. Accordingly, this rejection under 35 U.S.C. § 119(e) is moot.

Objection to the Specification

The Examiner objects to the specification because of informalities such as typographical and grammatical errors. Applicants have amended the specification to correct these informalities. Accordingly, Applicants request withdrawal of the objection to the specification.

Rejection of Claims 5 and 16 Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 5 and 16 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner is of the opinion that "[t]he term "analog" in claims 5 and 16 is indefinite because it is not defined either in the description or the art. It is not clear what degree of functional or

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structural similarity is necessary for one compound to be considered an analog of another compound."

Applicants respectfully traverse and request reconsideration. Claims 5 and 16 are directed to methods or compositions of the invention comprising a peptide wherein the peptide is a mastoparan or an analog thereof. Applicants respectfully submit that the term "analog" is well-known and widely used in the art as referring to compounds which are structurally similar to a particular compound, and have the same or substantially the same activity as the compound, but differ slightly in composition. Thus the phrase "mastoparan or an analog thereof" would be clearly understood by those of ordinary skill in the art. Furthermore, at page 8, lines 4-6, Applicants incorporate by reference U.S. Patent No. 5,589,568, wherein various analogs of mastoparans are specifically described at columns 4-6. In addition, at page 3, lines 15-17 and Example 2 of the instant specification, Applicants specifically describe an inactive analog of mastoparan, *i.e.*, MAS-17, and compare its activity with that of mastoparan. The term "analog" is therefore sufficiently definite based on both the meaning provided by Applicants' disclosure and the meaning understood in the art.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 5 and 16 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1-3, 6-9 and 11-14 Under 35 U.S.C. § 102(b)

The Examiner rejects claims 1-3, 6-9 and 11-14 under 35 U.S.C. § 102(b) as being anticipated by Bertics *et al.* Specifically, the Examiner is of the opinion that "Bertics *et al.* teach reducing the deleterious effects of endotoxin and endotoxic shock including LPS-induced shock by administering a 2-alkylthioadenosine-5'-nucleotide which blocks both LPS-induced GTPase activity and TNF production."

Applicants respectfully traverse and request reconsideration. As amended, claims 1-3, and 6-9 are directed to a method for treating or preventing septic shock in a subject comprising, administering to the subject an effective amount of an agent which binds G protein, to thereby inhibit the interaction of said G protein with CD14, such that septic shock in the subject is treated or prevented. Claims 11-14 are directed to a composition for treating or preventing septic shock in a subject comprising an effective amount of an

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agent which binds G protein to thereby inhibit the interaction of said G protein with CD14, such that septic shock in the subject is treated or prevented.

Bertics *et al.* teach that 2-MeS-ATP blocks the toxic effects of LPS by inhibiting the LPS-purinoreceptor interaction. (Column 5, lines 20-30) Specifically, Bertics *et al.* teach that "purinoreceptors are important for endotoxin action and a purine analog can prevent endotoxic death in mice." (Column 6, lines 51-53) Bertics *et al.*, however, do not teach the means by which 2-MeS-ATP inhibits LPS mediated toxicity and, instead, state that the mechanism by which 2-MeS-ATP acts is unknown. (Column 6, lines 41-49)

Applicants invention is based on the interaction between LPS and the GPI anchored glycoprotein CD14 receptor, not the purinoreceptor. Furthermore, Applicants demonstrate for the first time that CD14 on monocytes/macrophages physically interacts with hetereotrimeric G proteins. Thus, Applicants teach the specific mechanism by which the CD14 receptor mediates LPS mediated toxicity, *i.e.*, CD14 interacts with G proteins, these G proteins then regulate LPS induced MAP kinase activation and cytokine production in human monocytes/macrophages. (See page 2, lines 23-29 of the instant specification) In contrast, Bertics *et al.* teach a method of mediating LPS induced toxicity through a different receptor, *i.e.*, a purinoreceptor, and do not teach the mechanism by which the purinoreceptor acts to mediate LPS induced toxicity. Thus, Bertics *et al.* neither teach or suggest the present invention, *i.e.*, methods or compositions for treating or preventing septic shock in a subject comprising administering an effective amount of an agent which binds G protein, to thereby inhibit the interaction of said G protein with CD14.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 6-9 and 11-14 under 35 U.S.C. § 102(b).

Rejection of Claims 10 and 17 Under 35 U.S.C. § 103(a)

The Examiner rejects claims 10 and 17 under 35 U.S.C. § 103(a) as being obvious over Bertics *et al.* Specifically, the Examiner is of the opinion that "Bertics *et al* teach that antibiotic treatment is a current therapy for treating gram negative bacteria, but does not teach the combination of an antibiotic with the nucleotide. It would have been

obvious to one of ordinary skill in the art at the time Applicants' invention was made to use a combination of the antibiotic and nucleotide taught by Bertics *et al.* to treat gram negative bacteria infection because it is prima facie obvious to use a combination of treatments where each treatment has been used individually to treat the same disease and where there is no indication of negative interaction between the treating agents."

Applicants respectfully traverse and request reconsideration. Claims 10 and 17 are directed to methods and compositions of the invention further comprising an antibiotic. As the Examiner is aware, to establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)).

As set forth above, Bertics *et al.* do not teach the methods and compositions of the present invention. Thus, Bertics *et al.* also do not teach, suggest or motivate the invention claimed in claims 10 and 17, *i.e.,* a method or composition for treating or preventing septic shock in a subject comprising, administering to the subject an effective amount of an agent which binds G protein, to thereby inhibit the interaction of said G protein and CD14, such that septic shock in the subject is treated or prevented, further comprising an antibiotic.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 10 and 17 under 35 U.S.C. § 103(a).

Rejection of Claims 1-9 and 11-16 Under 35 U.S.C. § 102(b)

The Examiner rejects claims 1-9 and 11-16 under 35 U.S.C. § 102(b) as being anticipated by Higashijima *et al.* Specifically, the Examiner is of the opinion that "Higashijima *et al.* teach methods and compositions for modulating

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the action of G proteins. Mastoparan analogs are used. . . .With respect to claims 1-9, because the same active agent is being administered to the same subject by the same method steps, inherently septic shock will be prevented in Higashijima *et al.* to the same extent claimed by Applicants. With respect to claims 11-16, a suggested use limitation does not impart novelty or non-obviousness to a composition claim where the composition is otherwise taught or suggested by the prior art."

Applicants respectfully traverse and request reconsideration. Higashijima *et al.* teach methods and compositions for modulating the action of G proteins through mastoparans and mastoparan anlogs. However, as the Examiner acknowledges, Higashijima *et al.* do not teach that their method is useful for the treatment of septic shock. Contrary to the Examiner's assertion, one of ordinary skill in the art would not have used Higashijima *et al.*'s methods to treat septic shock because Applicants were the first to demonstrate that G proteins are involved in septic shock, *i.e.,* that LPS mediated toxicity results from the LPS receptor, CD14's, interaction with G proteins. Thus, without the benefit of Applicants' disclosure, one of ordinary skill in the art would not have used G protein modulators for the treatment of septic shock. In fact, the only diseases mentioned in Hagashima *et al.* are asthma, ulcers, cardiovascular diseases and Parkinson's disease. Furthermore, neither LPS, the relationship between LPS and G proteins, or the relationship between G proteins and CD14 is disclosed in Hagashima *et al.*

As the Examiner is aware, the Federal circuit has held that an anticipatory reference cited under 35 U.S.C. § 102(b) must be enabling, *i.e.,* it "must sufficiently describe the claimed invention to have placed the public in possession of it." (*Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys.*, 231 USPQ 649 (Fed. Cir. 1986).) Here, Higashijima *et al.* do not provide an enabling disclosure for the treatment of septic shock. Hagashima *et al.* merely provide methods of modulating G protein activity which would not have been used by the ordinarily skilled artisan for the treatment of septic shock without the benefit of Applicants' disclosure.

Accordingly, Applicants request reconsideration and withdrawal of the rejection of claims 1-9 and 11-16 under 35 U.S.C. § 102(b).

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Rejection of Claims 1-9 and 11-16 Under 35 U.S.C. § 102(b)

The Examiner rejects claims 1-9 and 11-16 are under 35 U.S.C. § 102(b) as being anticipated by Cabeza-Arvelaiz *et al.* Specifically, the Examiner is of the opinion that "[t]he Cabeza-Arvelaiz *et al.* article teaches the use of pertussis toxin and cholera toxin to inhibit the effects of LPS. The toxins antagonize LPS activation of G proteins. . . .The toxins constitute analogs of mastoparan because of the toxins have the same function and effect as mastoparan in treating or prevent septic shock, and because the claims do not set forth any structural limitations on what constitutes an analog of mastoparan."

Applicants respectfully traverse and request reconsideration. Cabeza-Arvelaiz *et al.* teach that pertussis toxin and cholera toxin are capable of inhibiting the effects of LPS. Contrary to the Examiner's assertion, pertussis and cholera toxins do not fall under the scope of the term "analog of mastoparan" as referred to in the pending claims and the instant specification. As set forth above, the term "analog" is well known and widely used in the art as referring to compounds which are structurally similar to the subject compound, and have the same or substantially the same activity as the compound, but differ slightly in composition. Thus, mastoparan analogs are compounds which are structurally similar to mastoparan. For example, U.S. Patent No. 5,589,568 (which is incorporated by reference into the instant specification) states that mastoparan analogs are compounds other than naturally occurring mastoparans which contain a mastoparan analog region and retain a mastoporan general structure. (Column 5, lines 10-12) Thus, Applicants submit that based on the teachings of the instant specification and the general knowledge in the art, the ordinarily skilled artisan would have known that pertussis and cholera toxins are not mastoparan analogs.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-9 and 11-16 under 35 U.S.C. § 102(b).

Rejection of Claims 10 and 17 Under 35 U.S.C. § 103(a)

The Examiner rejects claims 10 and 17 under 35 U.S.C. § 103(a) as being obvious over Cabeza-Arvelaiz *et al.* Specifically, the Examiner is of the opinion that "[t]he Cabeza-Arvelaiz *et al* article teaches that antibiotic treatment is a current therapy for LPS-induced shock, but does not teach the combination of an antibiotic with the

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toxin. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use a combination of the antibiotic and toxin taught by the Cabeza-Arvelaiz *et al.* article to treat gram negative bacteria infection because it is prima facie obvious to use a combination of treatments where each treatment has been used individually to treat the same disease and where there is no indication of negative interaction between the treating agents."

Applicants respectfully traverse and request reconsideration. Claims 10 and 17 are directed to methods and compositions of the invention further comprising an antibiotic. As set forth above, Cabeza-Arvelaiz *et al.* do not teach the methods and compositions of the present invention because pertussis toxin and cholera toxin are not encompassed by the term "analog of mastoparan". Moreover, Cabeza-Arvelaiz *et al.* specifically state that although the antibiotic pentoxifylline (an agent which inhibits turn-over of cAMP) has been found to be able to prevent sepsis, which suggests that the cAMP pathway is of critical importance in lethal LPS-induced pathology, their own work did not corroborate this suggestion since cAMP-raising agents used in their work failed to mimic the effects of the toxins they showed inhibited LPS-mediated toxicity. (page 133, paragraph 6) This is the only reference to antibiotics made Cabeza-Arvelaiz *et al.* Accordingly, contrary to the Examiner's assertion, Cabeza-Arvelaiz *et al.* teach away from using antibiotics in conjunction with methods and compositions of the invention used for treating or preventing septic shock in a subject. Thus, this reference does not provide the motivation, suggestion or expectation of success for treating septic shock by including an antibiotic with the methods and compositions of the invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 10 and 17 under 35 U.S.C. § 103(a).

Rejection of Claims 1-3, 6-9 and 11-14 Under 35 U.S.C. § 102(b)

The Examiner rejects claims 1-3, 6-9, and 11-14 under 35 U.S.C. 102(b) as being anticipated by Proctor *et al.* Specifically, the Examiner is of the opinion that "[t]he Proctor *et al.* article teaches administration of 2-methylthio-ATP to protect mice from endotoxic death. The 2-methyl-ATP antagonizes LPS activation of G proteins."

Applicants respectfully traverse and request reconsideration. Proctor *et al.* teach that the compound 2-methlythio-ATP inhibits the endotoxin stimulated release of toxic mediators by inhibiting the LPS-purinoreceptor interaction. (page 6019, column 2) The present invention, however, is based on the interaction between LPS, the GPI anchored gylcoprotein CD14 receptor, and heterotrimeric G proteins. Although Procter *et al.* teach that they "cannot rule out non-purinoreceptor effects that may be caused by 2-MeS-ATP", they state that the mechanism by which 2-MeS-ATP acts to inhibit LPS mediated toxicity is unknown. (page 6020, column 2) In contrast, Applicants specifically teach and claim that the LPS receptor CD14 which is present on monocytes/macrophages physically interacts with hetereotrimeric G proteins, and thus, these G proteins regulate LPS induced MAP kinase activation and cytokine production in human monocytes/macrophages. (See page 2, lines 23-29) Thus, Procter *et al.* is neither an enabling disclosure nor do they teach or suggest the now claimed invention, *i.e.*, methods or compositions for treating or preventing septic shock in a subject comprising administering an effective amount of an agent which binds G protein, to thereby inhibit the interaction of said G protein with CD14.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-3, 6-9 and 11-14 under 35 U.S.C. § 102(b).

Rejection of Claims 11 and 14-16 Under 35 U.S.C. § 102(b)

The Examiner rejects claims 11 and 14-16 under 35 U.S.C. §102(b) as being anticipated by Solomon *et al.* Specifically, the Examiner is of the opinion that "[t]he Solomon *et al* abstract teaches G protein agonists or antagonists such as mastoparan. . . . Note that a suggested use limitation does not impart novelty or non-obviousness to a composition claim where the composition is otherwise anticipated by or obvious over the prior art."

Applicants respectfully traverse and request reconsideration. The priority date for the instant application is September 5, 1997. The Solomon *et al.* abstract, which is Applicants' own work, was published on September 16, 1997 and, therefore, is not available as a § 102(b) reference. (M.P.E.P. § 2133). Moreover, Applicants respectfully submit that the citation of Solomon *et al.* is improper as a § 102(b) reference because it

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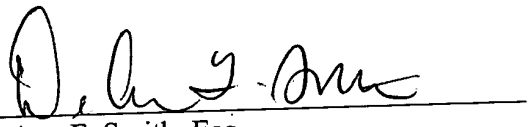
not enabling. As set forth above, the Federal Circuit has held that an anticipatory reference cited under 35 U.S.C. § 102(b) must be enabling, *i.e.*, it "must sufficiently describe the claimed invention to have placed the public in possession of it." (*Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys.*, 231 USPQ 649 (Fed. Cir. 1986).)

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 11 and 14-16 under 35 U.S.C. §102(b).

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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